

Deep Insight Section

Glutathione S-Transferase pi (GSTP1)

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Running title: GSTP1 review

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Pi-class glutathione-S-transferase (GSTP1) located on chromosome 11q13 encodes a phase II metabolic enzyme that detoxifies reactive electrophilic intermediates. GSTP1 plays an important role in protecting cells from cytotoxic and carcinogenic agents and is expressed in normal tissues at variable levels in different cell types. Altered GSTP1 activity and expression have been reported in many tumors and this is largely due to GSTP1 DNA hypermethylation at the CpG island in the promoter-5'.

We review the potential novel role of glutathione S-transferase pi (GSTP1) and its related expression in miscellaneous cancers. We focus on the rationale for use of molecular assays for the detection of cancer, emphasizing the role of the identification of epigenetic alterations. Finally, we focus on the potential role of GSTP1 in the pathway of prostate cancer, the most GSTP1 DNA hypermethylation-related neoplasm studied to date.

Advances in the epigenetic characterization of cancers enabled the development of DNA methylation assays that may soon be used in diagnostic testing of serum and tissue for cancers. Inhibition of aberrant promoter methylation could theoretically prevent carcinogenesis. Reactive oxygen species that are generated by physiologic processes such as cellular respiration, exposure to chemical agents, or exposure to ionizing radiation may overcome cellular antioxidant defense and cause DNA damage (Bostwick et al., 2000). Such damage may result in mutations and alteration of oncogenes or tumor suppressor genes. The cytosolic isoenzyme glutathione S-transferase pi (GSTP1) is an important multifunctional detoxifying enzyme within

the glutathione S-transferase family enzymes that inactivates electrophilic carcinogens by conjugation with glutathione (Toffoli et al., 1992; Jerónimo et al., 2001). The regulatory sequence near the GST gene is commonly affected by hypermethylation during the early stages of carcinogenesis (Lee et al., 1994; Brooks et al., 1998; Cairns et al., 2001; Jerónimo et al., 2002; Henrique and Jerónimo, 2004).

Several classes of GST, including alpha, mu, pi, and theta, were previously found in human tissue. For example, compared with benign tissue, there is increased expression of GST pi in cancers of the breast, colon, stomach, pancreas, bladder, lung, head and neck, ovary, and cervix, as well as soft tissue sarcoma, testicular embryonal carcinoma, meningioma, and glioma (Niitsu et al., 1989; Randall et al., 1990; Kantor et al., 1991; Satta et al., 1992; Toffoli et al., 1992; Green et al., 1993; Inoue et al., 1995; Bentz et al., 2000; Tratche et al., 2002; Simic et al., 2005; Arai et al., 2006).

However, hypermethylation of the GSTP1 promoter has been associated with gene silencing in prostate cancer and kidney cancer (Lee et al., 1994; Brooks et al., 1998; Cairns et al., 2001; Jerónimo et al., 2002; Dulaimi et al., 2004). Similarly, expression of GSTP1 is lower in invasive pituitary tumors than in noninvasive pituitary tumors and methylation status correlates with significant downregulation of GSTP1 expression; the frequency of GSTP1 methylation being higher in invasive pituitary tumors with reduced-GSTP1 expression than in pituitary adenomas with normal or high GSTP1 expression. These data indicate that GSTP1 inactivation through CpG hypermethylation is common in pituitary adenomas and may contribute to aggressive pituitary tumor behavior (Yuan et al., 2008). More recently, a study showed a trend of increasing GSTP1 methylation frequency with increasing grade of mammary phyllodes tumors. The

authors reported that GSTP1 promoter hypermethylation was associated with loss of GSTP1 expression. These results suggest that phyllodes tumors segregate into only two groups on the basis of their methylation profiles: the benign group and the combined borderline/malignant group (Kim et al., 2009). Other investigators studied the role of hypermethylation of the GSTP1 gene promoter region in endometrial carcinoma and found that reduced GSTP1 expression was associated with myometrial invasion potential (Chan et al., 2005).

Epigenetic alterations: emerging molecular markers for cancer detection

Cancer is a process fuelled both by genetic alterations and epigenetic mechanisms. Epigenetics refer to changes in gene expression that can be mitotically inherited, but are not associated with the changes in the coding sequence of the affected genes. In other words, epigenetics refer to the inheritance of information based on gene expression levels, in contrast to genetics that refer to transmission of information based on gene sequence (Esteller et al., 2000). DNA methylation, the best understood mechanism in epigenetics, is an enzyme-mediated chemical modification that adds methyl (-CH₃) groups at selected sites on DNA. In humans and most mammals, DNA methylation only affects the cytosine base (C), when it is followed by a guanosine (G). Methylation of the cytosine nucleotide residue located within the dinucleotide 5'-CpG-3' is the most frequent epigenetic alteration in humans. These CpG dinucleotides are not randomly distributed in the genome. Indeed, there are CpG-rich regions called "CpG islands" frequently associated with the 5' regulatory regions of genes, including the promoter. DNA methylation in the promoter regions is a powerful mechanism for the suppression of gene activity.

DNA methylation analysis: currently available methods

Methylation of CpG islands is of interest for diagnostic and prognostic reasons. Methylation of one or both alleles of a region can serve as a biomarker of cancer or silence gene expression when they are in a promoter region (Verma and Srivastava, 2002). Assays for methylation are appealing for translational research since they can utilize amplification techniques, such as methylation-specific polymerase chain reaction (PCR), and thereby utilize small amounts of samples.

Due to its relative simplicity, safety, and sensitivity, methylation-specific PCR is the most commonly employed method for methylation analysis (Herman et al., 1996).

The conventional methylation-specific PCR (CMSP) assay uses two sets of primers specifically designed to amplify the methylated or unmethylated sequence, and the PCR products are run in a gel (Herman et al., 1996). The results of CMSP at a particular DNA region are simply reported as methylated or unmethylated, not

allowing quantitation or identification of partial methylation. The CMSP assay is mainly used for GSTP1 methylation detection in fluids. For instance, GSTP1 methylation in serum of men with localized prostate cancer prior to treatment carries a 4.4 fold increased risk of biochemical recurrence following surgery (Bastian et al., 2005).

The use of fluorescence-based real-time quantitative methylation-specific PCR (QMSP) assay improved the sensitivity of tumor detection. Continuous monitoring of fluorescent signals during the PCR process enabled quantification of methylated alleles of a single region amongst unmethylated DNA because the fluorescence emission of the reporter represents the number of generated DNA fragments (Heid et al., 1996).

GSTP1 hypermethylation: significance and incidence related to prostate cancer

Epigenetic silencing of glutathione-S-transferase pi (GSTP1) is recognized as being a molecular hallmark of human prostate cancer. Methylation of CpG islands in the promoter of the pi class of glutathione S-transferase occurs in prostatic intraepithelial neoplasia (PIN) and cancer (Gonzalzo et al., 2004). Other hypermethylated regions relevant to prostate cancer include the retinoic acid receptor beta 2 (Bastian et al., 2007). These findings in prostate cancer suggest that DNA methylation is among the early events in tumorigenesis, but it remains to be seen whether DNA methylation is a necessary or permissive event in tumorigenesis.

The extensive methylation of deoxycytidine nucleotides distributed throughout the 5' "CG island" region of GSTP1 is not detected in benign prostatic epithelium, but has been detected in intraepithelial neoplasia, prostatic adenocarcinoma, and fluids (plasma, serum, ejaculate, and urine) of patients with prostate cancer by methylation-specific polymerase chain reaction assay, and may be useful as a cancer-specific molecular biomarker (Lee et al., 1994; Cairns et al., 2001; Henrique and Jerónimo, 2004; Crocitto et al., 2004; Perry et al., 2006; Hopkins et al., 2007; Cao and Yao, 2010).

Quantitative methylation-specific PCR (QMSP) reveals that the epigenetic silencing (loss of expression) of the GSTP1 gene is in fact the most common genetic alteration in prostate cancer (>90%) and high-grade prostatic intraepithelial neoplasia (PIN) (70%) (Lee et al., 1994; Brooks et al., 1998; Cairns et al., 2001; Harden et al., 2003; Henrique and Jerónimo, 2004) and this somatic inactivation ("silencing") of GSTP1 is directly associated with promoter methylation (Cairns et al., 2001; Jerónimo et al., 2002; Henrique and Jerónimo, 2004). Higher levels of GSTP1 promoter methylation is associated with the transition from prostatic intraepithelial neoplasia (PIN) to carcinoma (Henrique et al., 2006).

During cancer development, GSTP1 does not appear to function either as an oncogene or as a tumor suppressor

gene, since induced GSTP1 expression in prostate cancer cell lines failed to suppress cell growth. Instead, GSTP1 was proposed to act as a "caretaker" gene. When GSTP1 is inactivated, prostate cells appear to become more vulnerable to somatic alterations upon chronic exposure to genome-damaging stresses as oxidants and electrophiles, that are contributed by environment and lifestyle (Kinzler and Vogelstein, 1997; Cairns et al., 2001).

The significance of absent GSTP1 (GSTP1 silencing) in high grade PIN and carcinoma is unclear. It may be an epiphenomenon, simply reflecting disruption of the basal cell layer with neoplastic progression. However, Lee et al. considered the likelihood of a more fundamental role (Lee et al., 1994). Two studies found that a small proportion (3.5-5%) of cases retained modest GSTP1 expression in carcinoma (Cookson et al., 1997; Moskaluk et al., 1997). Cookson et al. also recorded positivity in 1 of 17 cases of high grade PIN (Cookson et al., 1997). Unlike genetic alterations that permanently and definitively change DNA sequence, promoter methylation is a potentially reversible modification. Hence, promoter methylation may be amenable to therapeutic intervention aimed at reactivating silenced cancer genes. This has important implications for chemoprevention because, as mentioned above, up to 70% of cases of high-grade PIN display GSTP1 promoter methylation (Brooks et al., 1998; Cairns et al., 2001; Jerónimo et al., 2002). Indeed, recently some authors have investigated the effects of green tea polyphenols (GTPs) on GSTP1 re-expression. They demonstrated that promoter demethylation by green tea polyphenols leads to re-expression of GSTP1 in human prostate cancer cells, therefore making green tea polyphenols excellent candidates for the chemoprevention of prostate cancer (Pandey et al., 2009).

Some investigators evaluated the impact of androgen deprivation therapy on the detection of GSTP1 hypermethylation in prostate cancer (Kollermann et al., 2006). In 87% (13/15) of the patients, there was no alteration in GSTP1 hypermethylation detection (Kollermann et al., 2006) and the authors suggested that the change from positive to negative GSTP1 hypermethylation status in two patients may point to partial androgen dependency (Kollermann et al., 2006). In addition to the supposed hormonal interaction, other possible explanations may be speculated to explain why prostate cancer loses GSTP1 hypermethylation after prolonged neoadjuvant hormonal therapy. First, the lack of GSTP1 hypermethylation may be attributable to technical problems (false negative results). Furthermore, the possibility that both tumors primarily lacked GSTP1 hypermethylation might be raised. However, further studies are necessary to assess the frequency and extent of hormonal interaction with GSTP1 hypermethylation.

Anti-cancer effect of GSTP1 and future prospects

Increased levels of GST pi may protect human cancer cells against cytotoxic drugs. Several antineoplastic drugs, particularly reactive electrophilic alkylating agents, form conjugates with glutathione spontaneously and in GST-catalyzed reactions (Awasthi et al., 1996). The expression of particular subclasses of GST protects cells from the cytotoxicities of these cancer drugs, and overexpression of GST has been implicated in antineoplastic drug resistance (Morrow et al., 1998). Induction of the enzymes is thought to represent an adaptive response to stress, and may be triggered by exogenous chemical agents and probably also by reactive oxygen metabolites (Hayes and Pulford, 1995). GST enzymes have a broad substrate specificity that includes substances with known mutagenic properties. Elevated serum GST pi has been exploited as a serum tumor marker for gastrointestinal cancer (Niitsu et al., 1989) and non-Hodgkin's lymphoma (Katahira et al., 2004) as a method of predicting sensitivity to chemotherapy.

Inactivation of GSTP1 in prostate cancer occurs early during carcinogenesis, leaving prostate cells with inadequate defenses against oxidant and electrophile carcinogens. Epigenetic mechanisms (see above) are strongly implicated in progression (Rennie and Nelson, 1998). Unlike genetic alterations, changes in DNA methylation are potentially reversible. Thus, therapeutic interventions involving reversal of the methylation process of several key genes in prostate carcinogenesis might improve current therapeutic options, thereby enhancing the anti-cancer effect of GSTP1 gene in patients "at risk" with high-grade PIN or in men with established prostate cancer. Nucleoside-analogue inhibitors of DNA methyltransferases, such as 5-aza-2'-deoxycytidine, are able to demethylate DNA and restore silenced gene expression. Unfortunately, the clinical utility of these compounds has not yet been fully realized, mainly because of their side effects. The anti-arrhythmia drug procainamide, a nonnucleoside inhibitor of DNA methyltransferases (category of enzymes that catalyze DNA methylation during cell replication), reversed GSTP1 DNA hypermethylation and restarted GSTP1 expression in LNCaP human prostate cancer cells propagated in vitro or in vivo as xenograft tumors in athymic nude mice (Cairns et al., 2001). Some investigators tested the potential use of procaine, an anesthetic drug related to procainamide. Using the MCF-7 breast cancer cell line, they have found that procaine produced a 40% reduction in 5-methylcytosine DNA content as determined by high-performance capillary electrophoresis and total DNA enzyme digestion. Procaine can also demethylate densely hypermethylated CpG islands such as those located in the promoter region of the RAR beta 2 gene,

restoring gene expression of epigenetically silenced genes. This property may be explained by binding of procaine to CpG-enriched DNA. Finally, procaine also has growth-inhibitory effects in these cancer cells, causing mitotic arrest (Villar-Garea et al., 2003). Thus, procaine and procainamide are promising candidate agents for future cancer therapies based on epigenetics. Li et al. reported that GSTP1 was upregulated in the stromal compartment of hormone-independent prostate cancer, which may contribute to chemoresistance of advanced prostate cancer (Morrow et al., 1998).

Epidemiologic evidence has shown a reduced risk of prostate cancer in men consuming selenium, suggesting a role for antioxidants in protection against prostate carcinogenesis. A systematic review and meta-analysis of the literature confirm that selenium intake may reduce the risk of prostate cancer (Etminan et al., 2005). Vitamin E intake also may decrease DNA damage and inhibit transformation through its antioxidant function. Long-term supplementation with alpha-tocopherol substantially reduced prostate cancer incidence and mortality in male smokers (Heinonen et al., 1998). Therapy directed at the induction or preservation of GSTP1 activity in benign prostatic epithelium may prevent or delay progression of prostatic cancer.

GSTP1 has a protective role as an antioxidant agent in transformation and progression of prostate cancer. The interplay between altered or impaired expression of GST appears to play a significant role in carcinogenesis in the prostate. Inhibition of aberrant promoter methylation could be an effective method of chemoprevention.

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